DETAILED ACTION

This application is a 371 (national stage application) of PCT/BE04/00172, filed on 12/2/04.

Priority

This application is a 371 (national stage application) of PCT/BE04/00172, filed on 12/4/04. The filing date of the instant application is 5/31/06. This application claims priority to the following foreign applications: 2451798, filed on 12/2/03; 03447279.5, filed on 12/2/03; 04447001.1, filed on 1/5/04; 04447066.4, filed on 3/18/04; 2461248, filed on 3/18/04; 04025035.9, filed on 10/21/04; 2004-349085, filed on 11/4/04; and 2487529, filed on 11/15/04. Certified copies of the foreign priority applications have been received. The instant application is also a continuation in part of the following applications: 10725965, filed on 12/2/03; 10/752423, filed on 1/6/04; and 10803793, filed on 3/18/04. Application No. 10/725965, 10/752423, and 10803793 provide support to the instant claims. Therefore, the priority and effective filing date given to the instant claims is that of the earliest filed application, 12/2/03.

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the

previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 7/14/2010 has been entered.

Response to Remarks

2. Claims 86, 94, 105-106 and 108 have been cancelled as of the response filed on 8/12/2010, and new claims 110-142 are currently pending.

Newly submitted claims 141-142 are directed to a method of treating a mood and an anxiety disorder in a patient. In the reply filed on 4/3/2009, Applicants had elected the pharmaceutical composition as the invention to be examined. Claims 110-140, which are directed to a pharmaceutical composition comprised of pipamperone in a dose from 5 to 15 mg, and escitalopram in a dose from 10 to 20 mg, have been included for examination. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 141-142 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

The claim amendments are sufficient to overcome the rejection under 35 USC 112, first paragraph; this rejection is withdrawn.

Applicant's arguments, with regards to the rejection under 35 USC 103(a) as being unpatentable over Cremers et. al., WO 01/41701 publication in view of Van Oekelen et. al., have been fully considered but are not found persuasive. The Applicant has stated that the non-obvious, unexpected results for the

combination of low dose pipamperone and citalopram have been acknowledged by the US Patent Office in applications 10/725965 (now US Patent No. 7,884,096) and 10/752423 (now US Patent No. 7,855,195). The Applicant has stated that these unexpected results are applicable to the instant application, as escitalopram is the (S)-stereoisomer of citalopram. The examiner has considered this argument, but it is not found persuasive. The showing of unexpected results for the combination of low dose pipamperone and citalopram is not found to be applicable to the instant claims, which are directed to a pharmaceutical composition comprised of low dose pipamperone and escitalopram. While it is acknowledged that escitalopram is the (S)-stereoisomer of citalopram, the Applicant has not shown how the unexpected results for the combination between pipamperone and citalopram would also correlate to the combination of pipamperone and the specific enantiomer, escitalopram. The examiner will consider data with respect to the combination of pipamperone and escitalopram, within the dosage range as claimed. The claimed invention of a pharmaceutical composition comprised of pipamperone between 5 to 15 mg., and escitalopram between 10 to 20 mg. would have been prima facie obvious to one of ordinary skill in the art, at the time of the invention, because Cremers et. al. teaches the combination of escitalopram and a compound having 5-HT_{2c} antagonistic, partial agonistic, or inverse agonistic activity for treating psychiatric and psychological conditions, while Van Oekelen et. al. teaches that pipamperone is a 5-HT antagonist which has binding affinity for both the 5-HT_{2A} and 5-HT_{2c} receptors, and is well known in the art for treating psychiatric conditions. Therefore, it would

have been obvious to have combined pipamperone with escitalopram, because pipamperone is taught by Van Oekelen as a 5-HT antagonist and has binding affinity for both the 5-HT_{2A} and 5-HT_{2c} receptors, and Cremers et. al. teaches the combination of a 5-HT_{2c} antagonist or inverse agonist and escitalopram. The rejection under 35 USC 103(a) was proper; in consideration of the new claims, a modified rejection under 35 USC 103(a) has been made, which will be discussed in detail in the office action.

The rejection for obviousness type double patenting over the claims of previously co-pending application 10/725965 has been withdrawn in consideration of the amended claims.

3. Claims 110-140 were examined.

4. Claims 110-140 are rejected.

Claim Rejections-35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 110-140 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cremers et. al., WO 01/41701 patent publication, in view of Van Oekelen et. al., *Eur. J. Pharm.*, **425**, pp. 21-32 (both of previous record), and further in view of Sanchez et. al., WO 01/03694.

The claims are directed to a pharmaceutical composition comprised of (a) pipamperone in a dose from 5 to 15 mg.; (b) escitalopram in a dose from 10 to 20 mg., for the treatment of a mood or anxiety disorder.

Cremers et. al. teaches a composition comprised of an SSRI and a compound having 5-HT_{2c} antagonistic, partial agonistic, or inverse agonistic activity (Abstract; p. 4, lines 9-15). Specifically, Cremers et. al. teaches escitalopram as the SSRI (p. 6, line 29; p. 11, lines 4-6; p. 12, lines 4-8). Treatment of depression, anxiety and affective disorders, impulse control disorders, panic, and other psychiatric conditions is taught (p. 4, lines 22-28). Unit dosage forms are taught (p. 6, lines 19-20). Cremers et. al. teaches that the combination of a 5-HT_{2C} receptor antagonist and a serotonin reuptake inhibitor results in a significant level of serotonin in comparison to administration of the serotonin reuptake inhibitor by itself (p. 9, lines 27-30), and allows for faster onset of the therapeutic benefit of the SSRI (p. 10, lines 6-8). It is also taught that the combination of a 5-HT_{2C} receptor antagonist and a serotonin reuptake

inhibitor reduces the amount of SSRI necessary for treatment, and decreases the side effects associated with the SSRI (p. 10, lines 10-15). Therapeutically effective dosages of the 5-HT_{2C} receptor antagonist are taught to range from about 0.1 to 150 mg/day, with preference to dosages between 0.5 to 50 mg/day and 1 to 5 mg/day (p. 14, lines 26-29).

Cremers et. al. does not explicitly teach that the compound having 5-HT_{2c} antagonistic, partial agonistic, or inverse agonistic activity is pipamperone, or that the amount of pipamperone to be administered is a unitary dose between 5 and 15 mg., and the dose of escitalopram is between 10-20 mg.

Van Oekelen et. al. teaches that pipamperone is a 5-HT antagonist and has binding affinity for both the 5-HT_{2A} and 5-HT_{2c} receptors (p. 25, Table 2; p. 27, left column, last paragraph; p. 29, left column, last paragraph-right column, top paragraph; p. 30, left column, 1st full paragraph). Van Oekelen et. al. also teaches that pipamperone has been widely used for therapeutic use (p. 29, right column, top paragraph).

It is not explicitly taught by Cremers et. al. nor Van Oekelen et. al. that the dose of escitalopram is from 10-20 mg.

Sanchez et. al. teaches escitalopram for the treatment of neurotic disorders, including anxiety and panic disorders (Abstract; p. 1, lines 5-9). Escitalopram is taught to be especially effective for treating anxiety, as well as panic attacks and other neurotic disorders (p. 2, lines 10-12). Pharmaceutical compositions comprising escitalopram are taught (Abstract; p. 4, lines 12-18).

Unit dosage forms are taught, with the dose of escitalopram ranging from about 1 to 50 mg/day, with preference of 10 to 20 mg/day (p. 4, lines 20-22).

One of ordinary skill in the art would have been motivated to combine pipamperone with escitalopram, because pipamperone has been known in the art to be widely used in compositions for psychiatric therapeutic purposes and functions as a serotonin antagonist, with binding affinity for both the 5-HT_{2A} and 5-HT_{2C} receptors, as taught by Van Oekelen et. al. (p. 25, Table 2; p. 27, left column, last paragraph; p. 29, left column, last paragraph-right column, top paragraph; p. 30, left column, 1st full paragraph), while escitalopram at a dose of 10 to 20 mg/day is taught to be effective for treating neurotic disorders, including anxiety and panic disorders. Cremers et. al. teaches a composition comprised of escitalopram and an additional compound that functions as a 5-HT_{2C} antagonist, partial agonist, or inverse agonist. While Cremers et. al. does not explicitly teach pipamperone as the 5-HT_{2C} antagonist, it is taught that the composition is comprised of a compound that functions as a 5-HT_{2C} antagonist, partial agonist, or inverse agonist (Abstract), and that this compound includes "antipsychotics having effect at 5-HT_{2C} receptors" (p. 12, lines 10-18). Van Oekelen et. al. teaches that pipamperone has an antagonistic effect on the 5-HT_{2C} receptor (p. 25, Table 2; p. 27, left column, last paragraph; p. 29, left column, last paragraph-right column, top paragraph; p. 30, left column, 1st full paragraph). Additionally, pipamperone has been commonly used for therapeutic purposes related to treatment of depression, anxiety, and other related disorders. Cremers et. al. also teaches that the combination of a 5-HT_{2C} antagonist with an SSRI such as

escitalopram results in increased therapeutic effectiveness of the SSRI when compared to the effects of the SSRI administered solely, as well as that the combination results in fewer side effects than typically observed with SSRI administration. As such, it would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to combine pipamperone with escitalopram, because Cremers et. al. teaches that escitalopram and an anti-depressant which has activity as an antagonist at the 5-HT_{2C} receptor are effective in compositions for treating depression and other anxiety disorders, and Van Oekelen teaches pipamperone as an antagonist for the 5-HT_{2C} receptor which is widely used for treatment.

It is noted that while Cremers et. al. does not explicitly state that the amount of pipamperone administered is a unitary dose between 5 to 20 mg., it is taught that the amount of 5-HT_{2C} antagonist, partial agonist, or inverse agonist to be administered ranges from 0.1 to 150 mg. daily, with preference to dosage ranges between 0.5 to 50 mg/day and 1 to 5 mg/day (p. 14, lines 26-29). While the claimed dose of pipamperone is from 5 to 15 mg., this dosage range is included within the effective dosages taught by Cremers et. al. for a 5-HT_{2C} antagonist, partial agonist, or inverse agonist. Particularly, Cremers et. al. teaches that low dosages, such as from 0.5 to 50 mg/day and 1 to 5 mg/day are effective. Therefore, it would have been prima facie obvious to one of ordinary skill in the art, in consideration of the teachings of Cremers et. al., to have established an optimum dosage range of pipamperone that is within the claimed dosage range of between 5 to 15 mg. Daily administration is taught. While it is

not explicitly taught that the composition is formulated for twice daily administration, it would have been prima facie obvious to one of ordinary skill in the art that as it is not taught that the composition is limited to once daily administration, administration of more than once per day, such as twice per day, would have been acceptable. Cremers et. al. and Sanchez et. al. both teach daily administration; therefore, it would have been obvious to have prepared the pharmaceutical composition for twice daily, in addition to once daily administration.

Claim Rejections-35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 134-137 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 134-137 recite the limitation of a pharmaceutically acceptable salt of pipamperone or escitalopram. However, these claims are dependent upon claims 110 and 113, which do not cite pharmaceutically acceptable salts. There is insufficient antecedent basis for this limitation in the claims.

Information Disclosure Statement

10. The information disclosure statements (IDS) submitted on 7/14/2010; 8/12/2010; and 9/28/2010 were filed after the mailing date of the final office action on 4/14/2010. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Conclusion

11. No claim is currently found allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 7:00 AM - 5:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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S.P.

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